Health Care Manag Sci (2013) 16:300–313
DOI 10.1007/s10729-013-9225-3

What is the value of 'me-too' drugs?

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Received: 21 October 2012 / Accepted: 14 February 2013 / Published online: 26 February 2013

Abstract The objective of this article is to estimate the value of 'follow-on' or 'me-too' drugs from the payer, industry and societal perspectives. Since me-too drugs do not bring additional clinical benefits, they are only valuable to payers if they save costs. An empirical model was constructed to identify the factors affecting whether a me-too drug results in cost savings to the pharmaceutical budgets of payers. These factors included the intensity of promotional spending, price discount and time to entry. Twenty-seven second-entrant products with limited differentiation were identified; their launch dates ranged from 1988 to 2009. On average, me-too drugs launch 2.5 years after the first entrant, with 20 % more promotional investment, and capture 38 % of market share within 4 years. Peak market share is significantly affected by share of voice ($p<0.001$) but not price discount ($p=0.77$). Launch delay was significant in terms of reducing both market share ($p<0.001$) and price ($p<0.05$). With a launch price 15 % below the incumbent, cumulative savings from use of a me-too drug peak at over $1000 million, but decrease rapidly after the first entrant becomes generic and only amount to $450 million over the me-too drug's lifecycle. With a price discount less than 10 %, cumulative savings are negative over the life of the me-too drug. Therefore, me-too drugs may be cost saving in the short term, but can represent a cost in the longer term. From a societal perspective, me-too drugs always decrease the economic surplus if they do not grow the market. If me-too drugs grow the market by 20 %, they augment, on average, the economic surplus only if the variable costs (including promotional investment) do not increase by more than $300 million per year.

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Keywords Follow-on drugs · Cost savings · Peak share · Share of voice · First-mover advantage

MSC codes 62J05 · 62P20 · 90B50

1 Introduction

Over recent decades, numerous new treatments have been developed for diverse medical conditions such as hypertension, hypercholesterolemia, cancer and HIV. Between 1990 and 2004, 431 new molecular entities were approved by the US Food and Drug Administration (FDA) [1]. Some compounds were genuine innovations, while others provided limited incremental therapeutic value over existing products. The former are often referred to as 'breakthrough' drugs, 'first-in-class' or 'innovators', while the latter are called 'incrementally modified' drugs, 'follow-on' drugs or, more often, 'me-too' drugs. In fact, the FDA assessed that 183 (42 %) of the 431 new molecular entities were "significant improvement[s] compared to marketed products" and the remaining 248 (58 %) appeared to "have therapeutic qualities similar to those of one or more already marketed" [1].

Given their limited incremental clinical benefits and their number, understanding the value of me-too drugs is critical for pharmaceutical companies when making research and development (R&D) decisions. As development costs can reach approximately $800 million per drug, pharmaceutical companies must often make trade-off decisions in their R&D portfolios [2]. Forecasting the potential of me-too drugs is important for informing resource-allocation decisions. Understanding the value of such drugs is also critical for payers (e.g. health insurers) when making reimbursement decisions; for physicians and patients when electing treatment choice and allocating healthcare spending; and for society when improving efficiency by directing healthcare resources to the most cost-effective uses.

1.1 Background

Me-too drugs lack innovation compared with existing therapeutic options and have been widely criticised in the general press [3] and the scientific literature on a number of grounds. For example, it has been argued that they divert R&D investment away from diseases with higher unmet needs [4] and may even damage innovation by reducing incentives to pioneer new therapeutic classes because me-too drugs curb the innovator's profits [5]. Pharmaceutical companies have been criticised for increasing spending on direct-to-consumer (DTC) advertising of me-too drugs, which has been perceived as tending to promote drugs over a healthy lifestyle and may lead to overconsumption [6]. Follow-on drugs may also limit the penetration of generics after the first-in-class drug is no longer protected by patent [7]. Me-too drugs can significantly augment expenditure growth. 80 % of the increase in drug expenditures between 1996 and 2003 in British Columbia could be explained by the use of drugs without clinical benefits over older drugs, most of which had lost patent [8].

Although increased competition from me-too drugs might be expected to lead to a decrease in price, this has not always occurred, which has led to criticism of the drug companies [9]. Azoulay found that in the histamine H_2-receptor antagonist market, Tagamet's price increased when Zantac, its first competitor, entered the market [10]. Additionally, Tagamet and Zantac prices continued to increase when other competitors were launched [10]. However, this study failed to account for the fact that potentially a higher price increase might have occurred without any new competition.

Conversely, it can be argued that me-too drugs have numerous positive effects. For example, they may provide improvements (albeit marginal) in treatment for some patients; there is evidence that for some diseases, patients do in fact respond differently to me-too drugs. For instance, although numerous randomized trials showed no significant differences in clinical effectiveness between selective serotonin reuptake inhibitor (SSRI) antidepressants, more than half of the patients who do not respond to one SSRI antidepressant benefit from another drug in the same class [11]. Notwithstanding the example of the H_2-receptor antagonist drugs discussed above, me-too drugs are typically introduced at a discount in the US and subsequent price increases are lower when there are more branded substitutes in the market [12]. Lexchin (2006) analysed 33 new me-too drugs in Canada and found that the mean introductory price was 8.5 % lower than the price of the most expensive brands [13]. Furthermore, payers are likely to use new entrants as a means to extract better value from the class via formulary management tools. For example, in a survey conducted in the USA most health plans stated that they would demand a 20 % discount compared with Advair to grant Dulera a favourable formulary position [14].

Although the name 'me-too' implies imitation, the existence of me-too drugs is more often due to parallel development [15]. Parallel development may stimulate competition to become the first company to launch a breakthrough product; this, in turn, could potentially accelerate development times and enhance product profiles [16]. Me-too drugs may also augment disease awareness through increased promotion such as DTC advertising. Such an increase in awareness may increase diagnosis rates, improve compliance and lead to better health outcomes. In addition, by affecting the first entrants' profits, the introduction of me-too drugs could potentially force innovators to invest more heavily in R&D to preserve revenue and profit growth. Although it has been argued that the development of me-too drugs diverts R&D investment away from diseases with higher unmet needs [4], it can also be argued that me-too drugs generate profits for manufacturers that can then be reinvested in R&D for disease states with high unmet needs.

Given the wide range of opinions regarding me-too drugs, an objective analysis of their impact is warranted. An analysis was conducted of the impact of me-too drugs across a wide range of therapeutic areas from the perspectives of pharmaceutical companies, payers and society. A me-too drug can offer cost savings to payers if introduced at a discount but can also increase costs if it has a higher price than the generic products once the pioneer loses the patent. The key objective of this paper is to identify whether the cost savings generated from a lower introductory price exceed the extra costs due to the slower adoption of generics after the pioneer loses patent. Additionally, the impact of me-too drugs on economic surplus is assessed.

In the next Section, the factors influencing the success and potential cost-savings of me-too drugs will be reviewed. Next, the data and the model used in the analysis will be explained and validated. Finally, the impact for payers, the pharmaceutical industry and society will be discussed.

2 Methods

2.1 Factors influencing the success of (me-too) drugs

Marketing literature has long identified that order of entry and quality of new products impact market success [17, 18]. Fischer and colleagues (2010) analysed the sales of pharmaceutical drugs and showed that a drug's quality increases peak sales and its order of entry reduces peak sales [19]. They also showed that a firm's own market expenditures positively impact sales while price had no impact. The impact of competitive marketing expenses is mixed in the literature. Prins and Verhoef (2007) found that promotional

investment spent by competitors reduces time-to-adoption [20] while Fischer and Albers (2010) [21] estimated that competitive marketing investments may have a category building effect and increase the sales of all brands in the market.

In this article, any given firm's expenditures and competitive expenditures are combined to calculate shares of promotional investment. Quality was not a relevant variable since it is similar between me-too drugs and innovators. The delay between launch of the innovator molecule and that of the me-too drug was used instead of order of entry. Additional factors considered were the duration of patent protection, price and the influence of managed care organisations.

2.2 Data sources

A number of governmental and proprietary datasets were used for the analysis, including:

1. Product evaluations by the Transparency Commission of the French national health authority – Haute Autorité de la Santé (HAS) [22];
2. US National Prescription Audit by Intercontinental Marketing Services (IMS), which measures the flow of prescriptions dispensed by pharmacies [23];
3. Promotional audit data for the USA from SDI Health, which tracks physician/nurse detailing, meetings and events, DTC advertising, and advertising in professional medical journals [24];
4. First Databank's National Drug Data File, which provides wholesaler acquisition costs (WACs) for the USA, also called ex-factory price [25]. The WAC is the list price paid by wholesalers or distributors to manufacturers before any discounts, rebates or allowances.

2.3 Model framework

2.3.1 Product selection

The order of market entry and level of differentiation were estimated for the major products manufactured by the largest pharmaceutical companies (Pfizer, Johnson & Johnson, Roche, Novartis, GlaxoSmithKline, Sanofi, AstraZeneca, Abbott Laboratories, Merck & Co., Bristol-Myers Squibb, Eli Lilly, Boehringer Ingelheim, Amgen, Genentech, NovoNordisk, Bayer,Takeda, Astellas, Daiichi Sankyo) using 2007, 2008 and 2009 annual reports. The annual reports provided information for products launched as far back as 1991. To avoid selection bias (namely only screening the most successful products of the major companies), all new molecular entities approved by the FDA from 1999[1] to 2007 were also analysed [26]. The dependent variable was the peak share over the first 4 years and recent launches could not be included. Finally, the branded versions of linisopril (Privinil and Zestril) were included in the sample since both brands were clinically undifferentiated. In the base model, Prinivil was the me-too of Zestril. In the Section 3.2., Zestril was the me-too of Prinivil. The analysis was limited to second-to-market drugs available in the USA.

Product differentiation was assessed based on Amélioration du Service Médical Rendu (ASMR; evaluation of therapeutic benefit) ratings used by the French Transparency Commission [22]. These ratings are an objective measure of the product's medical added value versus existing comparators, classified in five categories: ASMR I (therapeutic breakthrough), ASMR II (important improvement in terms of efficacy or safety), ASMR III (modest improvement in terms of efficacy or safety), ASMR IV (minor improvement in terms of efficacy or safety) and ASMR V (no improvement). The French ASMR is not the only system that evaluates drugs by assigning a rating. For instance, the German IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen) rating system also attempts to establish qualitative assessments of incremental value. The French rating system has several advantages. Firstly, all products in the sample had an ASMR rating at launch [27]. This is not the case with the German system since IQWiG was founded in 2004. Furthermore, French ratings are specifically designed to inform reimbursement and pricing decisions. Finally, they provide more information than the FDA ratings which are only distributed among 3 categories (priority review, standard review, orphan designation). In Section 4.5., the impact of using the FDA instead of the HAS ratings is analysed.

A product was classified as a me-too drug if it belonged to the same therapeutic class as a previous entrant and if its ASMR rating was IV or V. A second entrant was also classified as a me-too drug if it had the same ASMR rating as the first entrant when compared with an alternative therapeutic class (i.e. the first and second entrants were deemed to provide the same medical improvement vs an alternative therapy). In rare instances, products with a high ASMR rating were not considered to be me-too drugs if the market's perception differed widely from that of the HAS. Thus, Lyrica, Afinitor and Valtrex were not classified as me-too drugs for this analysis. In addition, a few me-too drugs (Lunesta, Effient) were launched shortly before the first entrant's generics and were therefore excluded from the analysis.

Finally, drugs dispensed via hospitals or specialty pharmacies, or which are administered intravenously in physicians' offices, were not included in the analysis as

[1] 1999 was chosen for convenience because the FDA web site does not provide electronic annual approval files before that date.

prescription information is not reliable for them. This data limitation excludes most hospital, oncology and biologic drugs from the analysis.

2.3.2 Price discount

Price discounts of me-to drugs at launch were estimated based on WACs in the USA [25].

2.3.3 Promotional investment

The share of voice (SoV) at launch was calculated. The SoV was defined as the relative portion of promotional investment of the new entrant within the two-product market composed of the incumbent and the me-too drug, according to the equation:

$$SoV_i = I_i / (I_i + I_j)$$

where SoV_i is the SoV of me-too drug i; I_i is the promotional investment (including resources spent on physician/nurse detailing, journals, events and DTC advertising) spent on me-too drug i over the first 12 months; and I_j is the promotional investment in the innovator drug j over the same period. A period of 12 months was chosen since Corstjens and colleagues (2005) showed that the sales performance over the first 4 quarters determines 81 % of the variance in sales in the long term [28]. The impact of the second year's promotional investment is estimated in the Section 3.3.

2.3.4 Market share

The number of prescriptions (TRx) was used to calculate monthly market share, which was defined as:

$$MS_{i,t} = TRx_{i,t} / (TRx_{i,t} + TRx_{j,t})$$

where $MS_{i,t}$ is the market share of me-too drug i during month t; $TRx_{i,t}$ is the number of prescriptions filled for me-too drug i during month t; and $TRx_{j,t}$ is the number of prescriptions of the innovator drug j during month t.

Since products have different adoption patterns and the time to reach their full potential varies, peak share was used for the analysis rather than the share per time period. As multiple events occur within the product's lifetime (such as new indications), peak share was calculated over the first 4 years of sales; therefore, peak share was defined as:

$$\underset{t \le 48\ m}{Max}\ MS_{i,t}$$

Different calculations were used in two particular cases: (1) average share over 4 years was used for products launched in the same quarter (e.g. Actos/Avandia; Zestril/Prinivil); (2) TRx for the first 4 years were not available for Zyrtec/Allegra, so share at 5 years was used.

2.3.5 Delay in launch of me-too drugs

The delay was expressed in quarters and capped at 15 quarters. The validation of this assumption is discussed in Section 2.6.

2.4 Core methodology

Cumulative savings for payers generated by me-too drugs were assessed using the equation:

$$C_i = \sum_t D_i * P_j * Share_{i,t} * MktTRx_{i,t} \quad (1)$$

where $Share_{i,t}$ is the share of me-too drug i during the period t; $MktTRx_{i,t}$ is the TRx in product i's market during the period t; P_j is the price of innovator j; and D_i is the price of me-too i relative to the innovator calculated as:

$$D_i = (P_i - P_i)/P_j$$

To estimate $Share_i$, the following regression was run:

$$Share_i = \alpha + \beta^* \ln(1 + SoV_i) + \gamma * T_i + \varepsilon_i \quad \text{with } \varepsilon_i \sim N(0, \sigma^2) \quad (2)$$

where SoV_i is the share of voice of me-too i at launch; T_i is the launch delay between product i and the innovator drug, and ε_i is the unobserved error term. Running the regression based on share (rather than actual prescriptions) avoids overweighting markets with high prescription volume. A logarithmic function for promotion was used because a decreasing return on promotion was expected.

To estimate price D_i, the following model was used:

$$D_i = D_0 + \lambda * T_i + \varepsilon'_i \quad \text{with } \varepsilon'_i \sim N(0, \sigma'^2) \quad (3)$$

where D_i is the price of product i at launch, relative to the innovator drug and ε'_i is the unobserved error term. Note that, over time, the relative price level may not remain constant. In particular, first and second entrants are unlikely to increase prices at exactly the same time. However, choosing to apply the discount at launch simplifies the analysis and the interpretation of the results.

The share and the price models could have been run concomitantly (using Eq. (1)). However, equation [2] was evaluated independently because the price is set before the peak market share is known. The impact of price on peak-share potential was analysed in the market-share model specification.

Regressions were run using the statistical analysis programs Stata (StataCorp LP, College Station, TX, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

2.5 Model validation

As the models rely on least-square estimates with a small number of observations, the following tests were used to ensure ordinary least-square assumptions for finite samples were not violated: (1) White test (homoscedasticity); (2) Ramsey RESET test (functional form of the conditional mean); (3) Shapiro–Wilk W test (normality of residuals); (4) variance inflation factor (absence of multicollinearity); (5) residuals versus predicted value plot (exogeneity).

2.6 Market-share model specification

A number of variables were added to the model, including the impact of price discounts and a comparison of the impact of SoV in the first and second years. It is conceivable that the longer a second entrant is delayed, the more important the SoV is in driving market share. Therefore, an interaction variable between launch delay and ln(1 + SoV) was introduced to test this hypothesis. An annual trend variable was included to elucidate whether the environment became more or less favourable for the me-too drugs over time.

In the core model, the impact of delay on market share was assumed to be a linear function when the launch delay was 15 quarters or less and was capped if the delay exceeded 15 quarters. With this assumption, once a certain level of delay was reached, an additional delay would not have a material impact on the potential of the me-too drug. A penalised spline regression was used to justify this assumption (data not shown).

2.7 Payer's perspective

The cost savings of me-too drugs as a function of price discount, launch timing and SoV were modelled in a market behaving similarly to the average market in the sample: TRx potential of approximately 6 million per quarter, innovator's WAC per TRx at $150 (median WAC/TRx for the sample was $133 and average price was $170 as of December 2009). The second entrant was assumed to launch with an average SoV derived from the sample. The launch delay (10 quarters) was also derived from the sample. Given the uncertainties regarding price discounts (see section 4), three price-discount levels were assumed for the second entrant: 5 % (similar to the average in the sample), 10 % and 15 %. Peak shares for all scenarios were estimated from the analysis described above.

Based on the sample, the first and second entrants were assumed to have become generic after 13 years on the market. Generic exclusivity was assumed to last for 6 months. After that, multiple generic products were assumed to have been launched. Generic versions of the first entrant were assumed to capture 95 % of the first entrant's TRx within a year (based on the generics' uptake of Zocor, Prilosec, Claritin and Flonase) but were assumed not to take market share away from the me-too drug. The final assumption reflects the historical lack of impact of generics on the non-generic brands [29].

During the generic exclusivity period (180 days), generic prices were assumed to be 15 % below that of the branded drug; afterwards, the price was assumed to decrease rapidly to 10 % of the branded drug's price. A 9 % discount rate was assumed for both pharmaceutical companies and private insurance companies [30].

Sensitivity analyses were conducted regarding launch delay, SoV, duration of patents (for innovators and me-too drugs) and the impact of the first entrant's generics on the sales of me-too drugs. No sensitivity analyses were conducted for discount rate, me-too uptake, generics pricing, market size or average price of the incumbent.

2.8 Societal perspective

The US health insurance market was assumed to be perfectly competitive and payers' savings were passed entirely on to consumers (otherwise, the zero-profit assumption is violated). The producer surplus is the excess of revenue over total variable costs [31]. When a second entrant decides to launch a me-too drug, the variable costs are related to promotional investment and product; however, the research and development costs are sunk and are not variable.

The economic surplus is the sum of the consumers' and producers' surplus: $\int_{P_1}^{P_0} D(P)dP + D_1 \cdot P_1 - D_0 \cdot P_0 - \Delta VC$ where D_0, P_0 are the average demand and price before the me-too is launched. D_1, P_1 are the average demand and price after the me-too is launched. ΔVC are the increase in variable costs generated by the launch of the second entrant.

2.9 Impact of me-too drugs on market growth

A before and after approach was used to assess new entrants' impact on market growth. Two monthly variables were introduced as independent variables: a time trend variable and a second variable that captured the new entrant's impact, which was zero before the new entrant launched and was increased by one unit per month after the new entrant launches. It was not possible to use this approach for all markets because the entry of a third or fourth product confounds the results in most markets. In addition, the time difference between the first and second entrants' launches was sometimes not sufficient to establish robust before and after trends.

3 Results

Overall, 27 products were identified as second entrants with limited differentiation (Table 1). The 'average' me-too drug was launched 2.5 years (10 quarters) after the first entrant, with a 54 % SoV and a 4 % WAC discount, and captured 38.5 % of market share.

The results of the regression analysis for Eqs. (2) and (3) are presented in Tables 2 and 3.

3.1 Peak market share

The impact of SoV on the peak market share is highly significant ($p<0.001$). An increase of 1 % in (1+SoV) leads, on average, to a peak share increase of 0.758 of a percentage point. The launch delay variable was found to be significant in both the market share model ($p<0.001$) and the price model ($p<0.05$). Each additional delay of one quarter reduced the peak share potential by 1.1 percentage points ($p<0.001$) and the price potential by 0.6 percentage points ($p<0.05$). Second-entrant delay (in quarters) multiplied by 1.1 % represents the actual first-mover advantage expressed in market-share points.

The model predicted an average peak share of 38.7 % (vs an actual share of 38.5 %; Table 1). A few products achieved a share substantially higher or lower than predicted: Zoloft (actual share +7 percentage points vs predicted), Reyataz (+7 points), Foradil (+6 points), Allegra D (+7 points), Femara (−11 points), Exelon (−9 points), Symbicort (−7 points), Onglyza (−6 points) and Zomig (−6 points).

If a product launched very late (e.g. 15 quarters later than the incumbent) without any promotional investment, one would expect its market share to be minimal and, indeed, the model predicted a peak share of less than 1 %.

3.2 Model validation

Results from the White, Ramsey and Shapiro–Wilk W tests ($p=0.47$, $p=0.25$ and $p=0.33$, respectively), the value of the variance inflation factor (1.0), and the lack of relationships between residuals and fitted values (Fig. 1), indicated that the ordinary least-square finite sample assumptions were not violated.

The results changed slightly when Zestril was assumed to be a me-too of Prinivil, The intercept was 0.15 ($p=0.02$) and the coefficient of the $\ln(1 + SoV)$ was 0.793 ($p=0.000$) and the coefficient for the launch delay did not change. The impact of removing the points whose leverage value was at least twice as high as the average is shown in Table 2. In practice, three observations (Prinivil/Zestril, Actos and Starlix) were removed. The significance and the magnitude of the coefficients of delay and SoV are comparable to those in Table 2. No observations were found to be influential (i.e. Cook's distance > 4/N, where N is the number of observations in the dataset).

3.3 Market share model specification

Table 2 presents the impact of adding covariates to the core model. Price discount was not found to be a significant variable for market share ($p=0.77$). SoV in the second year did not have a significant impact on the peak share potential ($p=0.42$). The time trend coefficient was negative but was only significant if the significance threshold was raised to 10 % ($p=0.063$). Given the low number of observations, a significance level of 10 % is acceptable. The sign of the trend variable showed that the first-in-class drug's advantage increased over time. When the interaction variable between launch delay and ln(1 + SoV) was introduced, ln(1 + SoV) and the interaction coefficients were not individually significant but were jointly significant (Chow test $p<0.001$). The interaction variable added marginal information to the core model (Akaike's Information Criterion [AIC] of −80.0 vs −78.2).

3.4 Payer's perspective: cost-saving estimates

Regardless of price discount assumptions, the cumulative savings from me-too drugs were found to be minimal in the first quarters because the second entrant's share was minimal (Fig. 2a). The cumulative, discounted savings peak occurred before the first entrant became generic, and were over $1000 million if the launch price was 15 % below the incumbent's price. After the first entrant becomes generic, the savings decrease because the second entrant becomes more expensive than the generics. Given the aggressive pricing strategies for generics, savings decreased rapidly and only amounted to $450 million over the me-too drug's lifecycle. If the price discount was less than 10 %, cumulative savings generated by the second product were negative over the lifetime of the me-too drug.

Assuming a 15 % price discount, the savings for payers from products launched with 69 % SoV were 18 % higher than those generated by products launched with 54 % SoV, while the savings from products launched with 39 % SoV were 20 % lower (Fig. 2b).

The results of the sensitivity analysis around launch delay are shown in Fig. 2c. Assuming a higher price discount for late entrants (0.6 % for each quarter; Table 3), late me-too drugs generated higher savings than early me-too drugs in the first few years but had less value over their lifetime.

The price discount necessary for a me-too drug to be cost saving was marginal if the me-too drug was launched a few quarters after the pioneer. However, if the me-too drug was delayed by 5 years, a price discount of 23 % CI: 17 %–35 % was necessary (Fig. 3). This is because the me-too drug prevents generic utilization for a long period after the first entrant

Table 1 'Me-too' drugs selected for analysis

1st entrant	2nd entrant	ASMR rating[a]	US launch	Launch delay (quarter)	Relative WAC at launch (%)	Peak share (%)	Launch SoV (%)
Celebrex	Vioxx	Same as Celebrex	May 1999	1	0	49	51
Imitrex	Zomig	None vs Imitrex	Dec 1997	15	−12	21	42
Claritin	Zyrtec	None vs Claritin	Jan 1996	11	−9	39	55
Cozaar	Diovan	V	Feb 1997	7	−3	48	68
Fosamax	Actonel	None vs Fosamax	Apr 2000	15	−10	33	53
Mevacor	Pravachol	Not available[b]	Nov 1991	15	−9	39	66
Prilosec	Prevacid	None vs Prilosec	May 1995	15	−8	37	54
Serevent	Foradil	None vs Serevent	May 2001	15	−8	31	38
Prozac	Zoloft	None vs Prozac	Feb 1992	15	−2	45	63
Aricept	Exelon	IV (same as Aricept)	May 2000	13	4	24	49
Avandia	Actos	V (same as Avandia)	Jul 1999	0	16	45	40
Zestril	Prinivil	Same molecule	Jan 1988	0	0	45	37
Risperdal	Zyprexa	IV vs Risperdal	Oct 1996	11	−6	45	58
Flonase	Nasonex	IV (same as Flonase)	Oct 1997	11	−2	42	54
Claritin D	Allegra-D	Same as Claritin D	Jan 1998	13	−18	34	37
Claritin	Zyrtec + Allegra	Same as Claritin	Jan 1996	11	−9	43	64
Viagra	Cialis + Levitra	V vs Viagra	Aug 2003	15	−5	44	70
Humalog	Novolog	V vs Humalog	Sep 2001	15	−8	23	37
Exforge	Azor	Same as Exforge	Oct 2007	1	−2	43	46
Concerta	M-CD + Add-XR	Similar molecule[c]	May 2001	3	0	54	74
Advair	Symbicort	IV (same as Advair)	Jun 2007	15	−11	20	43
Januvia	Onglyza	V (same as Januvia)	Aug 2009	11	0	31	53
Lantus	Levemir	Same as Lantus	Mar 2006	15	2	19	37
Sprycel	Tasigna	Same as Sprycel	Nov 2007	5	−16	50	69
Kaletra	Reyataz	Same as Kaletra	Jun 2003	11	23	49	63
Arimidex	Femara	Same as Arimidex	Jul 1997	6	0	36	63
Prandin	Starlix	Same as Prandin	Feb 2001	11	−6	50	86
	Average			10	−4	38	54
	Median			11	−5	42	54
	Minimum			0	−18	19	37
	Maximum			15	+18	54	86
	No. of observations			27	27	27	27

Sources: French HAS [22], IMS [23], SDI Health [24], First Databank [25]

ASMR Amélioration du Service Médical Rendu (evaluation of therapeutic benefit), *M-CD + Add-XR* Metadate CD + Adderall-XR, *SoV* Share of voice, *WAC* Wholesaler acquisition cost

[a] Same: the French HAS determined that the second entrant shares the same improvement benefits as the first entrant; None: HAS determined that the second entrant does not bring any additional benefits compared with the first entrant

[b] Pravachol was not evaluated against the first entrant (Mevacor) by HAS, since Mevacor was not launched in France. The author's judgement of ASMR rating was used

[c] Metadate CD and Concerta are both methylphenidate hydrochloride with extended release formulation. Concerta and Adderall XR have similar efficacy and side effects

loses patent. The number of years with patent protection is uncertain and varies across drugs, so a confidence interval for the required price discounts was created based on 20 000 simulations (1000 for each quarter of delay). The results of the simulations show that a price discount of up to 35 % may be required for a late me-too drug to be cost saving (Fig. 3).

Managed care organizations have become more aggressive in managing brands' prescriptions once an innovator loses patent. For instance, Lipitor's market share decreased by an additional 0.01 % (0.004 point) per month after Pravachol's generics were introduced (data not shown). When overlaying a similar share decrease for me-toos once the innovator lost

Table 2 Coefficient estimates: second-entrant peak share model results

	Basic model	Basic model without leverage	With price discount	With 2nd year SoV	With interaction	With time trend
Constant (%)	17.3**	9.7	17.2**	15.5*	34.5**	21.8***
Delay vs 1st entrant (%)	−1.1***	−0.9**	−1.1***	−1.2***	−2.8**	−1.1***
ln(1 + SoV) (%)	75.8***	87.6***	75.8***	68.7***	32.6	75.0***
$\ln(1 + \text{SoV}_{2\text{ndyear}})$ (%)				12.8		
Price discount (%)			4.1			
Delay*ln(1 + SoV) (%)					4.3	
Time trend (years) (%)						−0.4
Adjusted R^2	0.74	0.73	0.73	0.74	0.76	0.77
Observations	27	24	27	27	27	27

SoV Share of voice

*$p<0.05$; **$p<0.01$; ***$p<0.001$

patents, the results of the simulations showed that the a price discount of 21 % (95 % CI: 16 %–32 %) for a late me-too drug (i.e. delayed by 5 years). Therefore, managed care intervention only slightly increases the value of me-too drugs.

3.5 Impact of me-too drugs on market growth

The results of the analysis of new entrants' impact on market growth for the erectile dysfunction and the sleeping aid markets are presented in Table 4 and Fig. 4. In both markets, the before and after trend variables were highly significant. The erectile dysfunction market grew at a rate of 11 000 TRx per month and the sleeping aid market at 20 600 TRx per month before new entrants entered the market. However, the markets had opposite growth patterns after the new launches. The market growth increased by 30 500 TRx per month for the sleeping aid market but decreased by 7500 TRx per month in the erectile dysfunction market. One potential explanation for the decrease in TRx for erectile dysfunction drugs was a scare linking them to blindness in 2005 [32]. If the analysis was halted at the end of 2004, the trend after second entrant launch coefficient was positive but insignificant.

3.6 Societal perspective

Using the assumptions described in Section 2.7. and assuming that the me-too launch price is 15 % below the incumbent's price, the cumulative increase in consumer surplus is approximately $525 million regardless of the market growth (i.e. for sleep or erectile dysfunction markets). The change in producers' surplus depends on market growth assumptions. If the market does not grow, the producers' surplus decreases by $525 million plus any additional variable costs. The economic surplus always decreases since no incumbent decreased promotional investments when competition entered the market. If the market grows at the same rate as the sleep market (approximately 20 % incremental growth after 24 months), the producers' surplus grows by $3500 million minus any increase in variable costs. The launch of a me-too drug increases the economic surplus only if the increase in variable costs does not exceed $4075 million over the life of the me-too drug (i.e. approximately $300 million per year). This was not the case for the sleep market since SDI health reported that the promotional investments increased by $700 million a year after the introduction of me-toos.

Table 3 Coefficient estimates: second-entrant price model results

	Coefficient (%)	Standard error	*p*-value
Constant	2.5	0.033	0.451
Delay vs 1st entrant	−0.6*	0.003	0.041

$R^2 = 16$ %; adjusted $R^2 = 12$ %

*$p<0.05$

4 Discussion

4.1 Pharmaceutical companies' perspective

The model has enabled an objective analysis of several of the factors influencing the success of me-too drugs. A number of observations can be made based on the model's output.

Some products performed much better (or worse) in reality than predicted by the model. There could be a number of explanations for this, for example the ability to differentiate or the competition's focus.

With regard to the delay between launch of the first entrant and the me-too drug, the longer a second entrant is delayed, the less share it is likely to capture and the lower its

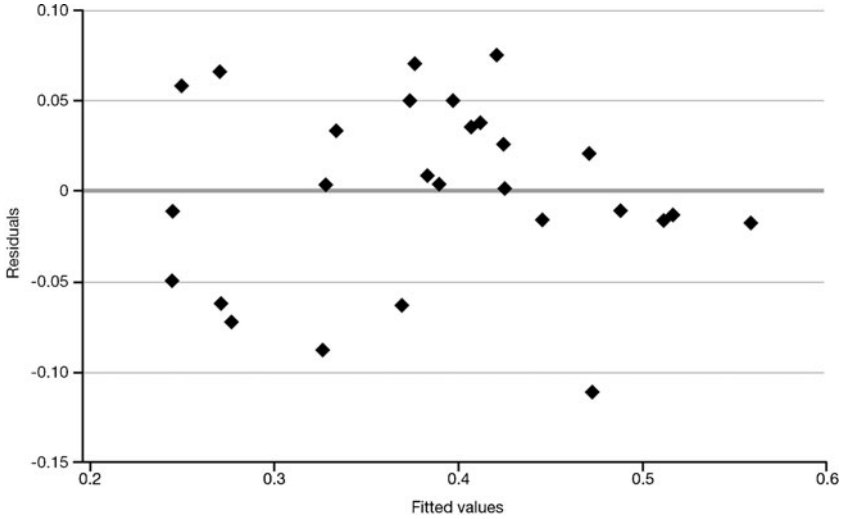

Fig. 1 Residuals versus predicted market shares

price. The first entrant is therefore better established, and the ability of a me-too drug to gain market share is reduced and payers are more likely to demand a lower price to reimburse the product.

It is possible for pharmaceutical companies to offset launch delays with an increased SoV to achieve a target market share. The required increase in SoV can be calculated by differentiating Eq. (2) assuming the peak share target remains constant. The formula to offset a delay is:

$$\mathrm{dSoV}/(1+SoV) = (-\gamma/\beta) * \mathrm{dT} \tag{4}$$

By using the regression coefficients in Table 2,

$$\mathrm{dSoV}/(1+SoV) = -1.48\% * \mathrm{dT} \tag{5}$$

For instance, a company planning to launch a me-too drug with a 50 % SoV and facing a one-quarter delay has to increase its SoV to 52.2 % to reach the same peak share that would have been achieved without the delay. Therefore, the company will have to increase the planned promotional investment by 9.2 %. Approval delays can therefore be very costly for companies.

It is worth noting that the constant in the price model is not significant: if the first entrant and the second entrant launch within the same quarter, prices are expected to be equivalent, which makes intuitive sense (Table 3).

The implications of the results presented in Tables 2 and 3 are fundamental for the pharmaceutical industry, if the results are generalized beyond the analysed time-frame (more on this in Section 4.2.3.). To gain market share, pharmaceutical companies should focus on promotional investments. Investing at the appropriate level over the first 12 months after launch greatly influenced the success of the drug. More specifically, the model can help pharmaceutical companies to determine the promotional investment that maximises profits and to understand whether investing in research for a me-too drug is commercially sound. As the adjusted R^2 in the peak share model is 0.74, other factors account for at most 26 % of the success. The level of promotional investment, rather than its quality, seems to matter most. This point is further discussed in Section 4.6.

4.2 Market share model specification

4.2.1 Price discount impact

Price discount was found not to be a significant variable for market share. In other words, it cannot be shown that increasing the price discount at launch helps a product to increase its market share potential. A feasible explanation is that physicians and patients are not usually exposed to the actual price of the drugs. In general, physicians do not pay for the drugs and patients' co-payments are typically not linked to drug prices (with the exception of co-insurance). Also, price cannot be considered as a competitive advantage as the price of the first entrant can easily be lowered to match that of the second entrant. The implication of this finding is that aggressive pricing is not recommended as it does not significantly impact share. However, managed care organisations seem to have become more aggressive in managing prices recently, and the impact of pricing decisions may increase in the future.

4.2.2 Share of voice: first year versus second year impact

Although the model predicted that a company's promotional investment level in the second year does not have a significant impact on the peak share potential, it should be noted that one cannot conclude that companies should only invest for 12 months and then stop promotion as no companies have experimented with such a promotional investment pattern.

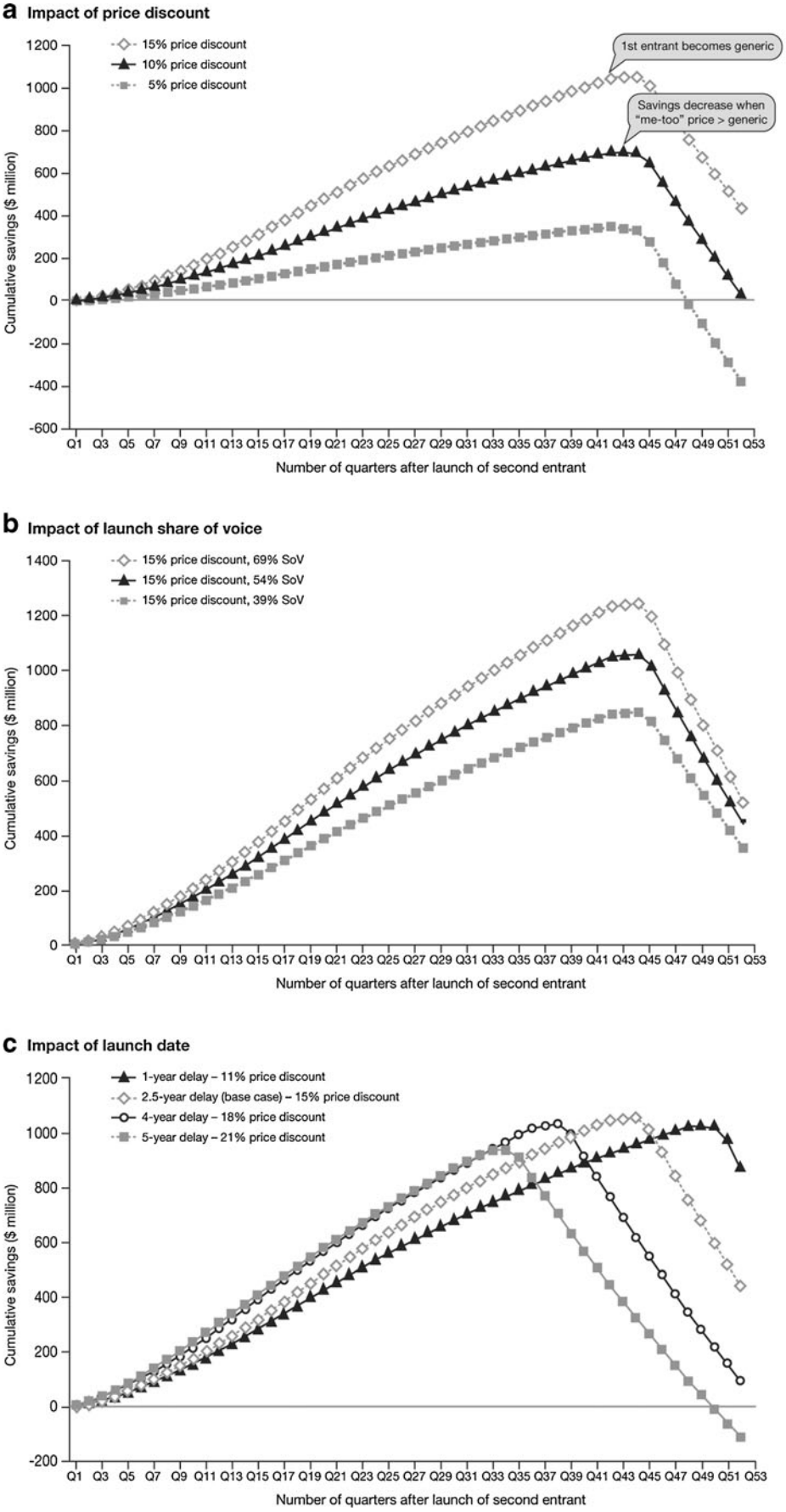

Fig. 2 Impact on payers' cumulative savings of (**a**) price discount, (**b**) launch share of voice, and (**c**) launch date

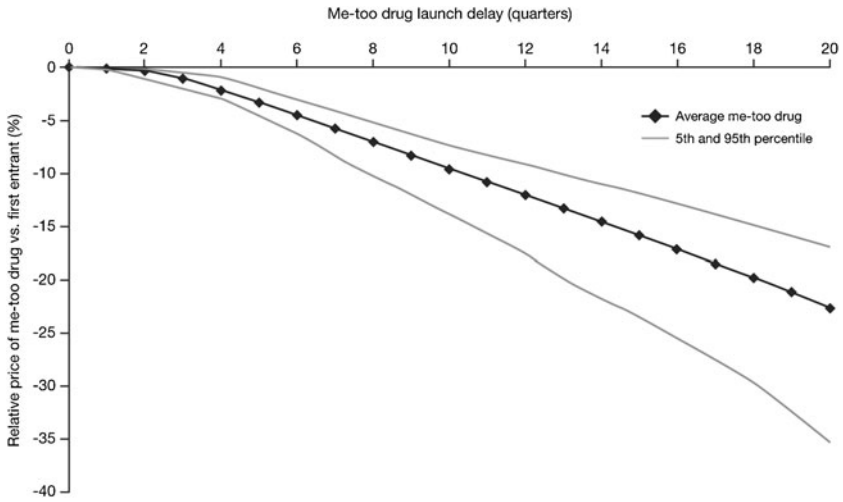

Fig. 3 Price discount required for a me-too drug to be cost saving

4.2.3 Time trend

The time trend coefficient was negative, meaning that the first in class's advantage increased over time. In other words, and with everything else being equal, it was better on average for a me-too drug to launch in the 1990s than in the 2000s. One potential explanation is the increasing impact of managed care organisations influencing sales. Over time, managed care organisations have become more and more effective in managing formularies and influencing physician's prescribing patterns. For instance, Express Scripts, one of the largest pharmacy benefit management companies in the USA, erased Lipitor from its list of preferred drugs in 2005 [33]. The intent was clearly to entice patients to use a competitor, Zocor (simvastatin), which was soon to become generic. It should be noted that the time trend coefficient is not significant. This may be due to the low number of products recently launched in the sample.

4.3 Payer's perspective

The median list price discount observed in the model (4 %) is not sufficient for a me-too drug to be cost saving. Additional rebates beyond the list price discount are necessary to ensure that savings are generated over the lifetime of the product.

As savings depend on SoV, price discount and launch delay, payers should consider these three variables when evaluating me-too drugs. For instance, they could calculate the rebates necessary to ensure that a new entrant will be cost saving over its lifecycle.

A late me-too drug represents an expensive alternative to the incumbent's generic over a longer timeframe. In particular, the cumulative savings are negative for me-too drugs launched 5 years after the first entrant, even if sold at a price 21 % below that of the first entrant, unless managed care organisations are able to drive generic utilisation in the market.

4.4 Impact on market growth

Market growth could represent a cost or a saving for payers. While incremental market growth generates additional drug costs, it could also represent a benefit if incremental usage is directed towards appropriate patients. The introduction of new sleeping aids considerably increased the size of the market but it is unclear whether this increase was driven by an increase in diagnoses of sleeping disorders or "disease

Table 4 Impact of new entrants on market growth (before and after analysis)

	Sleeping aid[a]	Erectile dysfunction[b]	Erectile dysfunction (until Dec 2004)
TRx constant (×1000)	2335.6***	1114.5***	1126.4***
Trend before 2nd entrant launch (TRx/month)	20.6***	11.0***	9.8***
Trend after 2nd entrant launch (TRx/month)	30.5***	−7.5***	1.6

TRx Number of prescriptions

***$p<0.001$

[a] Prais-Winsten regression was used to correct for the errors' serial correlation ["prais" procedure was used in Stata]

[b] A regression with robust estimator of variances was used to correct for heteroscedasticity ["vce(robust)" option was used in Stata]

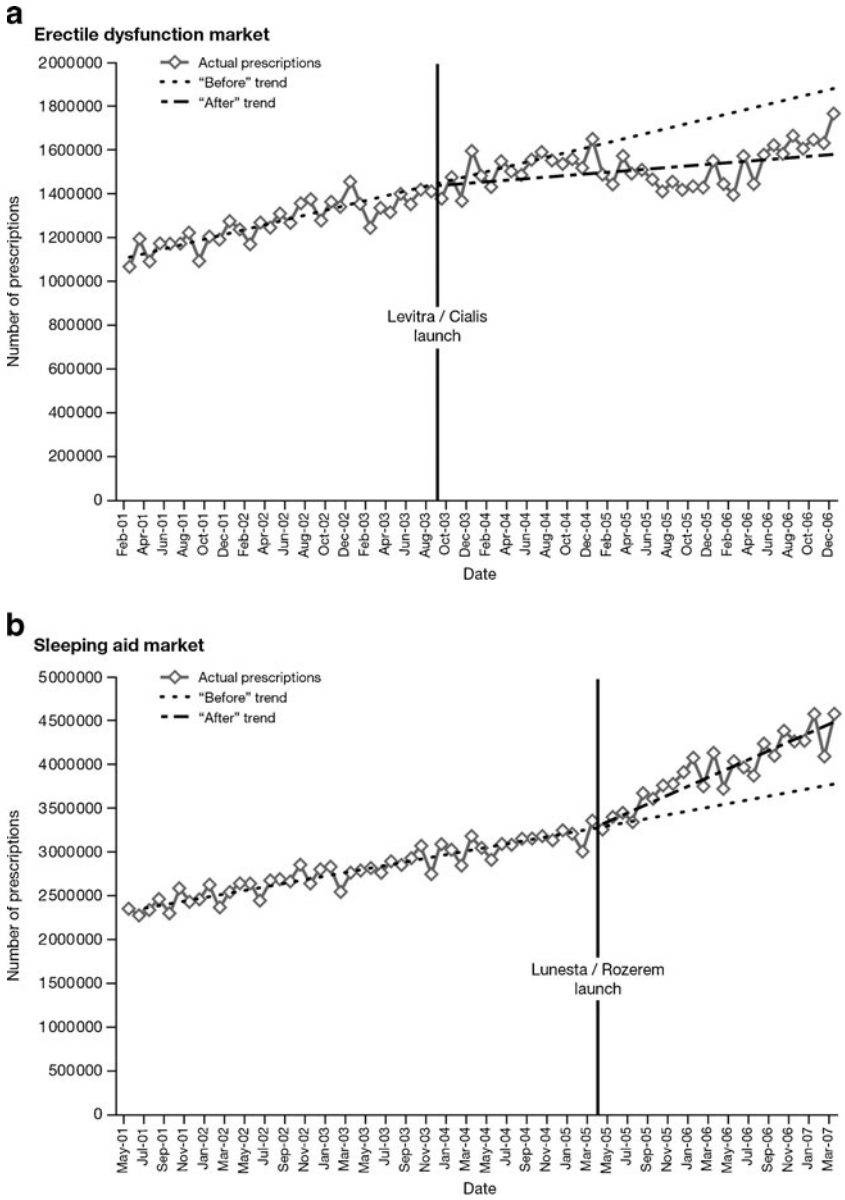

Fig. 4 Before-and-after analysis: impact of new entrants in (**a**) erectile dysfunction and (**b**) sleeping aid markets

mongering". The impact of DTC promotion can be seen as an insightful analogue. Some studies show that DTC advertising can increase compliance and the likelihood that patients receive the appropriate treatment [34, 35]. However, it might also increase overuse and off-label use [34].

4.5 Impact of using the FDA instead of the HAS ratings

Out of the 27 products in the sample, all but three went through the FDA's standard review process. The priority review status of Vioxx and Actos is not incompatible with a me-too classification since their approvals were within 1 month of Celebrex and Avandia. Kaletra would be excluded from the sample if the FDA classification was used.

All second entrants approved by the FDA from 1999 to 2007 were screened and classified as potential me-too drugs if they went through a standard review process were dispensed at a pharmacy and sales were reported. Inspra and Pylera were the only potential me-toos that were not included in the sample since Inspra received an ASMR of III (vs. Aldactone) and Pylera was not reviewed by the HAS. Therefore, using the HAS or FDA classifications did not dramatically alter the sample.

4.6 Limitations

Several caveats and shortcomings should be considered with regard to some of the data used in this study. Firstly, although ex-factory prices are publicly available, any rebates offered by manufacturers to secure reimbursement are not disclosed; therefore, the actual prices paid by payers cannot always be accurately assessed. In an effort to create a perception of differentiation, pharmaceutical companies try

to differentiate me-too drugs from existing options by targeting different patient segments or different points in the therapy algorithm, or by conducting DTC advertising.

The IMS and SDI Health data are based on sampling. A small sample size can make the estimate unstable, and caution should be used when interpreting SoV because the corresponding confidence intervals could be large.

As discussed above, me-too drugs may provide additional benefits to some patients and, therefore, may bring more than cost savings. However, the quantification of those benefits is not readily available and could not be incorporated in the model.

The model could suffer from the following biases: (1) Bias due to measurement. Survey data are prone to measurement error and the level of promotional investments may not be accurately recorded which would bias the regression coefficients downward. The model estimated share as a function of a constant, promotional investment, time delay and an error term ε. Quality of the promotional investment is not reported and, if quality impacts share, it is part of the error term ε. It is plausible that physicians might over-report the quantity of promotional investment for products with effective promotional campaigns. In other words, the quality (unmeasured) and the quantity (measured) of the promotional investment might be correlated. In that case, the error term ε and the independent variable (promotional investment) would be correlated. This would be a violation of the OLS assumptions and the regression coefficients would be biased. A possible solution to these issues is to gather data directly from pharmaceutical companies. (2) Causality bias. It was assumed that SoV drives market share but it is also plausible that manufacturers' expectations of market share drive launch promotional investment decisions. However, we do not believe that causality is an issue as it is unlikely that manufacturers can identify products with high potential share a priori, given the limited differentiation of me-too drugs.

The analysis was conducted for products sold in the retail channel. For products sold by specialty pharmacies or hospitals, the results may differ from those presented in this paper.

5 Conclusions

Me-too drugs have a substantial market impact and can represent considerable sales potential for pharmaceutical companies. On average, they launch with 20 % more resources than the incumbents and they capture 38 % of market share within 4 years. The model allowed an objective analysis of some of the factors that impact on the success or otherwise of me-too drugs. The peak market share depends on the promotional investment at launch and the length of the innovator drug's launch advantage. Me-too drugs are introduced at a reduced price compared to incumbent products. The magnitude of the discount depends on the delay between the launch of the incumbent and the me-too drug; however, the price discount does not have a significant impact on market share. In other words, manufacturers' pricing decisions within the customary range do not impact on the potential market share.

In certain circumstances, me-too drugs are cost saving for payers. Namely, price discounts have to be sufficient and me-too drugs have to be launched within a few years after the first entrant. If me-too drugs are launched late, they could save payers money in the short and medium term, but could represent a cost in the long term, as they prevent conversion to low-priced alternatives after the first entrant becomes generic. Managed care organisations can increase the overall value of me-too drugs by providing incentives to switch from me-too drugs to generic versions of the first entrants. The tactics used by some managed care organizations to convert Lipitor utilization to generic simvastatin can be used to increase the value of me-toos [33]. In all scenarios analysed, cost savings are small in the first 2 years of the me-too product's lifecycle. Therefore, if managed care organisations have a short-term financial focus, me-too drugs do not offer financial benefits and only provide additional treatment choices to physicians and patients.

To further assess the value of me-too drugs, a similar analysis could be conducted for hospital products and for products launched as third or fourth entrants into the market. A cross-sectional time-series analysis of R&D investment decision could shed more light on the impact that me-too drugs have on innovation.

Acknowledgments The author would like to thank Professor Claude Jeanrenaud, Institut de recherches économiques, Université de Neuchâtel, for helpful advice. Editorial assistance was provided by Dr Duncan Porter of Anthemis Consulting Ltd, funded by Novartis Vaccines & Diagnostics AG. Novartis also provided access to proprietary databases.

Funding The study reported in this paper was conducted as part of the author's research at the University of Neuchâtel. Novartis Vaccines & Diagnostics AG provided funding for editorial assistance in the writing of this article. The author is an employee of Novartis Vaccines & Diagnostics AG. This paper represents the view of the author and should not be considered as representative of the view of Novartis AG.

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